JUN 23 2000

NDA 20-509/S-005/S-008/S-009/S-010

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

We acknowledge the receipt of your October 6, 1998 submission containing final printed labeling (FPL) in response to our August 25, 1998 letter approving your supplemental new drug application for Gemzar (gemcitibine HCl).

We have reviewed the labeling that you submitted in accordance with our August 25, 1998 letter, and we find it acceptable.

We also refer to your supplemental new drug applications dated April 21, 1998 (S-008) and May 21, 1998 (S-009) received April 22 and May 22, 1998 respectively. Supplemental new drug application S-008 provides for draft revisions to the labeling for S-005 and was mistakenly processed as a new supplement. Supplemental new drug application S-009 provides for revisions to the ADVERSE REACTIONS section of the labeling. These supplements have been superseded by the FPL submitted October 6, 1998. Therefore, S-008 and S-009 will be retained in your tiles.

Finally, we refer to supplemental new drug application S-010, dated July 20, 1998 and received July 21, 1998, which provides for a revision in the ADVERSE REACTIONS, Pulmonary subsection of the labeling and which was not incorporated into the October 6, 1998 FPL. We have completed review of these supplemental new drug applications and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective as recommended in the final printed labeling submitted on October 6, 1998 with the revisions listed below from S-010.

1. In the ADVERSE REACTIONS section, Single-Agent Use subsection, Renal subsection, delete "as indicated by" following "microangiopathic hemolysis." This statement should now read:

   The diagnosis of Hemolytic-Uremic Syndrome (HUS) should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal

failure (elevation of serum creatinine or BUN).

2. In the ADVERSE REACTIONS section, Single-Agent Use subsection, Pulmonary subsection, delete "rarely" and modify to read:

> Pulmonary effects (including pulmonary edema, interstitial pneumonitis, or adult respiratory distress syndrome (ARDS), sometimes severe, have been reported in association with Gemzar therapy. The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

Accordingly, the supplemental new drug application (S-010) is approved effective as of the date of this letter.

Submit 20 copies of FPL as described above as soon as it is available, in no case more than 30 days after it is printed to each application. Individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-509/S-010." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

If you have any questions, contact Sean Bradley, Project Manager, at (301) 594-5750.

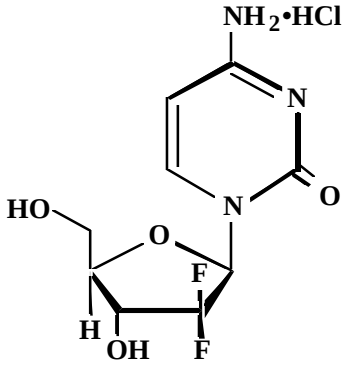
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

GEMZAR®
(GEMCITABINE HCl)
FOR INJECTION

DESCRIPTION

Gemzar® (gemcitabine HCl) is a nucleoside analogue that exhibits antitumor activity. Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (ß-isomer).

The structural formula is as follows:



The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4$ • HCl. It has a molecular weight of 299.66.

Gemcitabine HCl is a white to off-white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

CLINICAL PHARMACOLOGY

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin *in vitro*. No effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was observed. *In vivo*, gemcitabine showed activity in combination with cisplatin against the LX-1 and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-H520 xenografts. Gemcitabine was synergistic with cisplatin in the Lewis lung murine xenograft. Sequential exposure to gemcitabine 4 hours before cisplatin produced the greatest interaction.

Human Pharmacokinetics—Gemcitabine disposition was studied in five patients who received a single 1000 mg/m^2/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2'-deoxy-2',2'-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma. Gemcitabine plasma protein binding is negligible.

The pharmacokinetics of gemcitabine were examined in 353 patients, about 2/3 men, with various solid tumors. Pharmacokinetic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (<70 minutes) and long infusions (70 to 285 minutes). The total Gemzar dose varied from 500 to 3600 mg/m^2.

Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Clearance was affected by age and gender. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table 1 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 1
Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	Clearance Men (L/hr/m^2)	Clearance Women (L/hr/m^2)	Half-Life[a] Men (min)	Half-Life[a] Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

[a]Half-life for patients receiving a short infusion (<70 min)

Gemcitabine half-life for short infusions ranged from 32 to 94 minutes, and the value for long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose.

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes, indicating that gemcitabine, after short infusions, is not extensively distributed into tissues. For long infusions, the volume of distribution rose to 370 L/m^2, reflecting slow equilibration of gemcitabine within the tissue compartment.

The maximum plasma concentrations of dFdU (inactive metabolite) were achieved up to 30 minutes after discontinuation of the infusions and the metabolite is excreted in urine without undergoing further biotransformation. The metabolite did not accumulate with weekly dosing, but

its elimination is dependent on renal excretion, and could accumulate with decreased renal function.

The effects of significant renal or hepatic insufficiency on the disposition of gemcitabine have not been assessed.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

CLINICAL STUDIES

Non-Small Cell Lung Cancer (NSCLC)—Data from two randomized clinical studies (657 patients) support the use of Gemzar in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC.

Gemzar plus cisplatin versus cisplatin: This study was conducted in Europe, the U.S., and Canada in 522 patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received prior chemotherapy. Gemzar 1000 mg/m^2 was administered on days 1, 8, and 15 of a twenty-eight day cycle with cisplatin 100 mg/m^2 administered on day 1 of each cycle. Single-agent cisplatin 100 mg/m^2 was administered on day 1 of each 28-day cycle. The primary end point was survival. Patient demographics are shown in Table 2. An imbalance with regard to histology was observed with 48% of patients on the cisplatin arm and 37% of patients on the Gemzar plus cisplatin arm having adenocarcinoma.

The Kaplan-Meier survival curve is shown in Figure 1. Median survival time on the Gemzar plus cisplatin arm was 9.0 months compared to 7.6 months on the single-agent cisplatin arm (Logrank p=0.008, two-sided). Median time to disease progression was 5.2 months on the Gemzar plus cisplatin arm compared to 3.7 months on the cisplatin arm (Logrank p=0.009, two-sided). The objective response rate on the Gemzar plus cisplatin arm was 26% compared to 10% with cisplatin (Fisher's Exact p<0.0001, two-sided). No difference between treatment arms with regard to duration of response was observed.

Gemzar plus cisplatin versus etoposide plus cisplatin: A second, multicenter, study in Stage IIIB or IV NSCLC randomized 135 patients to Gemzar 1250 mg/m^2 on days 1 and 8, and cisplatin 100 mg/m^2 on day 1 of a 21-day cycle or to etoposide 100 mg/m^2 I.V. on days 1, 2, and 3 and cisplatin 100 mg/m^2 on day 1 on a 21-day cycle (Table 2).

There was no significant difference in survival between the two treatment arms (Logrank p=0.18, two-sided). The median survival was 8.7 months for the Gemzar plus cisplatin arm versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for the Gemzar plus cisplatin arm was 5.0 months compared to 4.1 months on the etoposide plus cisplatin arm (Logrank p=0.015, two-sided). The objective response rate for the Gemzar plus cisplatin arm was 33% compared to 14% on the etoposide plus cisplatin arm (Fisher's Exact p=0.01, two-sided).

Quality of Life (QOL): QOL was a secondary endpoint in both randomized studies. In the Gemzar plus cisplatin versus cisplatin study, QOL was measured using the FACT-L, which assessed physical, social, emotional and functional well-being, and lung cancer symptoms. In the study of Gemzar plus cisplatin versus etoposide plus cisplatin, QOL was measured using the EORTC QLQ-C30 and LC13, which assessed physical and psychological functioning and symptoms related to both lung cancer and its treatment. In both studies no significant differences were observed in QOL between the Gemzar plus cisplatin arm and the comparator arm.

Figure 1

Kaplan-Meier Survival Curve in
Gemzar plus Cisplatin versus Cisplatin NSCLC Study (N=522)

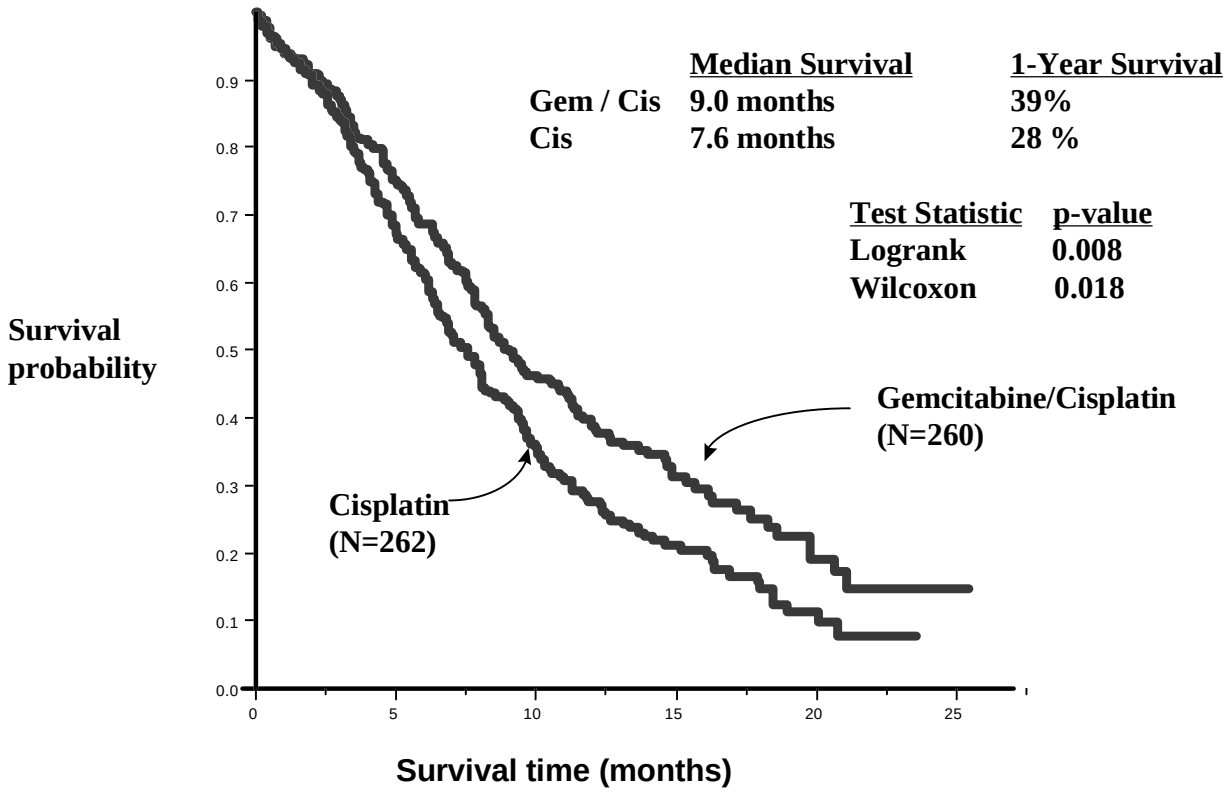


Table 2

Randomized Trials of Combination Therapy with Gemzar plus Cisplatin in NSCLC

Trial	28-day Schedule[a]			21-day Schedule[b]		
Treatment Arm	Gemzar/ Cisplatin	Cisplatin		Gemzar/ Cisplatin	Cisplatin/ Etoposide	
Number of patients	260	262		69	66	
Male	182	186		64	61	
Female	78	76		5	5	
Median age, years	62	63		58	60	
Range	36 to 88	35 to 79		33 to 76	35 to 75	
Stage IIIA	7%	7%		N/A	N/A	
Stage IIIB	26%	23%		48%	52%	
Stage IV	67%	70%		52%	49%	
Baseline KPS[c] 70 to 80	41%	44%		45%	52%	
Baseline KPS[c] 90 to 100	57%	55%		55%	49%	
Survival			p=0.008			p=0.18
Median, months	9.0	7.6		8.7	7.0	
(95% C.I.) months	8.2, 11.0	6.6, 8.8		7.8, 10.1	6.0, 9.7	
Time to Disease Progression			p=0.009			p=0.015
Median, months	5.2	3.7		5.0	4.1	
(95% C.I.) months	4.2, 5.7	3.0, 4.3		4.2, 6.4	2.4, 4.5	
Tumor Response	26%	10%	p<0.0001[d]	33%	14%	p=0.01[d]

[a]28-day schedule—Gemzar plus cisplatin: Gemzar 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin 100 mg/m^2 on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m^2 on Day 1 every 28 days

[b]21-day schedule—Gemzar plus cisplatin: Gemzar 1250 mg/m^2 on Days 1 and 8 and cisplatin 100 mg/m^2 on Day 1 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m^2 on Day 1 and I.V. etoposide 100 mg/m^2 on Days 1, 2, and 3 every 21 days

[c]Karnofsky Performance Status

[d]p-value for tumor response was calculated using the 2-sided Fisher's exact test for difference in binomial proportions. All other p-values were calculated using the Logrank test for difference in overall time to an event.

N/A Not applicable

Pancreatic Cancer—Data from two clinical trials evaluated the use of Gemzar in patients with locally advanced or metastatic pancreatic cancer. The first trial compared Gemzar to 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial studied the use of Gemzar in pancreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of Gemzar was administered intravenously at a dose of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatment with Gemzar. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks.

The primary efficacy parameter in these studies was "clinical benefit response", which is a measure of clinical improvement based on analgesic consumption, pain intensity, performance status and weight change. Definitions for improvement in these variables were formulated prospectively during the design of the two trials. A patient was considered a clinical benefit responder if either:

i) the patient showed a ≥50% reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consumption, or a twenty point or greater improvement in performance status

(Karnofsky Performance Scale) for a period of at least four consecutive weeks, without showing any sustained worsening in any of the other parameters. Sustained worsening was defined as four consecutive weeks with either any increase in pain intensity or analgesic consumption or a 20 point decrease in performance status occurring during the first 12 weeks of therapy.

OR:

ii) the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain (≥ 7% increase maintained for ≥ 4 weeks) not due to fluid accumulation.

The first study was a multi-center (17 sites in US and Canada), prospective, single-blinded, two-arm, randomized, comparison of Gemzar and 5-FU in patients with locally advanced or metastatic pancreatic cancer who had received no prior treatment with chemotherapy. 5-FU was administered intravenously at a weekly dose of 600 mg/m^2 for 30 minutes. The results from this randomized trial are shown in Table 3. Patients treated with Gemzar had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to 5-FU. The Kaplan-Meier curve for survival is shown in Figure 2. No confirmed objective tumor responses were observed with either treatment.

Table 3
Gemzar Versus 5-FU in Pancreatic Cancer

	Gemzar	5-FU	
Number of patients Male Female	63 34 29	63 34 29	
Median age Range	62 years 37 to 79	61 years 36 to 77	
Stage IV disease	71.4%	76.2%	
Baseline KPS[a] ≤70	69.8%	68.3%	
Clinical benefit response	22.2% (N[c] = 14)	4.8% (N = 3)	p = 0.004
Survival Median 6-month probability[b] 9-month probability[b] 1-year probability[b] Range 95% C.I. of the median	 5.7 months (N = 30) 46% (N = 14) 24% (N = 9) 18% 0.2 to 18.6 months 4.7 to 6.9 months	 4.2 months (N = 19) 29% (N = 4) 5% (N = 2) 2% 0.4 to 15.1+ months 3.1 to 5.1 months	p = 0.0009
Time to Disease Progression Median Range 95% C.I. of the median	 2.1 months 0.1+ to 9.4 months 1.9 to 3.4 months	 0.9 months 0.1 to 12.0+ months 0.9 to 1.1 months	p = 0.0013

[a]Karnofsky Performance Status

[b]Kaplan-Meier estimates

[c]N = number of patients

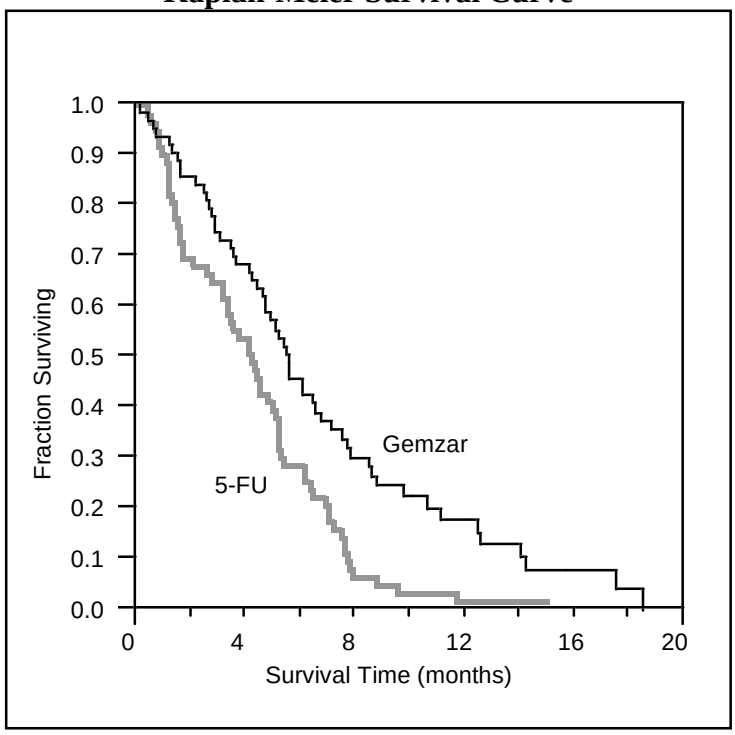
\+ No progression at last visit; remains alive.

The p-value for clinical benefit response was calculated using the 2-sided test for difference in binomial proportions. All other p-values were calculated using the Logrank test for difference in overall time to an event.

Clinical benefit response was achieved by 14 patients treated with Gemzar and 3 patients treated with 5-FU. One patient on the Gemzar arm showed improvement in all three primary parameters

(pain intensity, analgesic consumption, and performance status). Eleven patients on the Gemzar arm and two patients on the 5-FU arm showed improvement in analgesic consumption and/or pain intensity with stable performance status. Two patients on the Gemzar arm showed improvement in analgesic consumption or pain intensity with improvement in performance status. One patient on the 5-FU arm was stable with regard to pain intensity and analgesic consumption with improvement in performance status. No patient on either arm achieved a clinical benefit response based on weight gain.

Figure 2
Kaplan-Meier Survival Curve



The second trial was a multi-center (17 U.S. and Canadian centers), open-label study of Gemzar in 63 patients with advanced pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen. The study showed a clinical benefit response rate of 27% and median survival of 3.9 months.

Other Clinical Studies—When Gemzar was administered more frequently than once weekly or with infusions longer than 60 minutes, increased toxicity was observed. Results of a Phase 1 study of Gemzar to assess the maximum tolerated dose (MTD) on a daily x 5 schedule showed that patients developed significant hypotension and severe flu-like symptoms that were intolerable at doses above 10 mg/m^2. The incidence and severity of these events were dose-related. Other Phase 1 studies using a twice-weekly schedule reached MTDs of only 65 mg/m^2 (30-minute infusion) and 150 mg/m^2 (5-minute bolus). The dose-limiting toxicities were thrombocytopenia and flu-like symptoms, particularly asthenia. In a Phase 1 study to assess the maximum tolerated infusion time, clinically significant toxicity, defined as myelosuppression, was seen with weekly doses of 300 mg/m^2 at or above a 270-minute infusion time. The half-life of gemcitabine is influenced by the length of the infusion (*see* Clinical Pharmacology) and the toxicity appears to be increased if Gemzar is administered more frequently than once weekly or with infusions longer than 60 minutes (*see* Warnings). In a single trial, where Gemzar at a dose of 1000 mg/m^2 was

administered for up to six (6) consecutive weeks concurrently with therapeutic thoracic radiation to patients with NSCLC, significant toxicity in the form of severe, and potentially life-threatening, esophagitis and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy. The optimum regimen for safe administration of Gemzar with therapeutic doses of radiation has not yet been determined (*see* Precautions).

INDICATIONS AND USAGE

Therapeutic Indications

Non-Small Cell Lung Cancer—Gemzar is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer.

Pancreatic Cancer— Gemzar is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemzar is indicated for patients previously treated with 5-FU.

CONTRAINDICATION

Gemzar is contraindicated in those patients with a known hypersensitivity to the drug (*see* Adverse Reactions--Allergic).

WARNINGS

Caution—Prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing have been shown to increase toxicity (*see* Clinical Studies).

Gemzar can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anemia (*see* Adverse Reactions), and myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy. *See* Dosage and Administration for recommended dose adjustments.

Hemolytic-Uremic Syndrome (HUS) has been reported rarely with the use of Gemzar. (*See* Adverse Reactions--Renal)

Pregnancy—Pregnancy Category D. Gemzar can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. There are no studies of Gemzar in pregnant women. If Gemzar is used during pregnancy, or if the patient becomes pregnant while taking Gemzar, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

General—Patients receiving therapy with Gemzar should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents. Most adverse events are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced. There was a greater tendency in women, especially older women, not to proceed to the next cycle.

Laboratory Tests—Patients receiving Gemzar should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. Suspension or modification of therapy should be considered when marrow suppression is detected (*see* Dosage and Administration).

Laboratory evaluation of renal and hepatic function should be performed prior to initiation of therapy and periodically thereafter.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term animal studies to evaluate the carcinogenic potential of Gemzar have not been conducted. Gemcitabine induced forward mutations *in vitro* in a mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo* mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, *in vivo* sister chromatid exchange, and *in vitro* chromosomal aberration assays, and did not cause unscheduled DNA synthesis *in vitro*. Gemcitabine I.P. doses of 0.5 mg/kg/day (about 1/700 the human dose on a mg/m^2 basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. In female mice fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day I.V. (about 1/200 the human dose on a mg/m^2 basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day I.V. (about 1/1300 the human dose on a mg/m^2 basis).

Pregnancy—Category D. *See* Warnings.

Nursing Mothers—It is not known whether Gemzar or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from Gemzar in nursing infants, the mother should be warned and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the potential risk to the infant.

Elderly Patients—Gemzar clearance is affected by age (*see* Clinical Pharmacology). There is no evidence, however, that unusual dose adjustments, (i.e., other than those already recommended in the Dosage and Administration section) are necessary in patients over 65, and, in general adverse reaction rates in the single-agent safety database of 979 patients were similar in patients above and below 65. Grade 3/4 thrombocytopenia was more common in the elderly.

Gender—Gemzar clearance is affected by gender (*see* Clinical Pharmacology). In the single agent safety database (N=979 patients), however, there is no evidence that unusual dose adjustments (i.e., other than those already recommended in the Dosage and Administration section) are necessary in women. In general, in single agent studies of gemcitabine adverse reaction rates were similar in men and women, but women, especially older women, were more likely not to proceed to a subsequent cycle and to experience grade 3/4 neutropenia and thrombocytopenia.

Pediatric Patients—Gemzar has not been studied in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

Patients with Renal or Hepatic Impairment—Gemzar should be used with caution in patients with preexisting renal impairment or hepatic insufficiency. Gemzar has not been studied in patients with significant renal or hepatic impairment.

Drug Interactions—No confirmed interactions have been reported with the use of Gemzar. No specific drug interaction studies have been conducted.

Radiation Therapy—Safe and effective regimens for the administration of Gemzar with therapeutic doses of radiation have not yet been determined (*See* Clinical Studies).

ADVERSE REACTIONS

Gemzar has been used in a wide variety of malignancies, both as a single agent and in combination with other cytotoxic drugs. The following discussion focuses on single agent use where the effects of Gemzar can be most readily determined and on the specific combination use that is the basis for its use in NSCLC.

Single-Agent Use: Myelosuppression is the principal dose-limiting toxicity with Gemzar therapy. Dosage adjustments for hematologic toxicity are frequently needed and are described in the Dosage and Administration section.

The data in Table 4 are based on 979 patients receiving Gemzar as a single-agent administered weekly as a 30-minute infusion for treatment of a wide variety of malignancies. The Gemzar starting doses ranged from 800 to 1250 mg/m^2. Data are also shown for the subset of patients with pancreatic cancer treated in 5 clinical studies. The frequency of all grades and severe (WHO grade 3 or 4) adverse events were generally similar in the single-agent safety database of 979 patients and the subset of patients with pancreatic cancer. Adverse reactions reported in the single-agent safety database resulted in discontinuation of Gemzar therapy in about 10% of patients. In the comparative trial in pancreatic cancer, the discontinuation rate for adverse reactions was 14.3% for the gemcitabine arm and 4.8% for the 5-FU arm.

All WHO-graded laboratory events are listed in Table 4, regardless of causality. Non-laboratory adverse events listed in Table 4 or discussed below were those reported, regardless of causality, for at least 10% of all patients, except the categories of Extravasation, Allergic, and Cardiovascular and certain specific events under the Renal, Pulmonary, and Infection categories. Table 5 presents the data from the comparative trial of Gemzar and 5-FU in pancreatic cancer for the same adverse events as those in Table 4, regardless of incidence.

Hematologic—In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity with Gemzar, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during Gemzar therapy and dosage modified or suspended according to the degree of hematologic toxicity (*see* Dosage and Administration).

Gastrointestinal—Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

Hepatic—Gemzar was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemzar or with greater total cumulative dose.

Renal—Mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the hemolytic uremic syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving Gemzar in clinical trials. Four patients developed HUS on Gemzar therapy, two immediately post-therapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis as indicated by elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemzar therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

Fever—The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemzar may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash—Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.

Pulmonary—Dyspnea was reported in 23% of patients, severe dyspnea in 3%. Dyspnea may be due to underlying disease such as lung cancer (40% of study population) or pulmonary manifestations of other malignancies. Dyspnea was occasionally accompanied by bronchospasm

(<2% of patients). Rare reports of parenchymal lung toxicity consistent with drug induced pneumonitis have been associated with the use of Gemzar. Rarely pulmonary edema of unknown etiology, sometimes severe, has occurred in association with Gemzar therapy. Gemzar therapy should be discontinued immediately and appropriate supportive care measures instituted.

Edema—Edema (13%), peripheral edema (20%) and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.

Flu-like Symptoms—"Flu syndrome" was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

Infection—Infections were reported for 16% of patients. Sepsis was rarely reported (<1%).

Alopecia—Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity—There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

Extravasation—Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. Gemzar is not a vesicant.

Allergic—Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemzar should not be administered to patients with a known hypersensitivity to this drug (*see* Contraindication).

Cardiovascular—Two percent of patients discontinued therapy with Gemzar due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these patients had a prior history of cardiovascular disease.

Table 4
Selected WHO-Graded Adverse Events in Patients Receiving Single Agent Gemzar
WHO Grades (% incidence)

	All Patients[a]			Pancreatic Cancer Patients[b]			Discontinuations (%)[c]
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Patients
Laboratory[d]							
Hematologic							
Anemia	68	7	1	73	8	2	<1
Leukopenia	62	9	<1	64	8	1	<1
Neutropenia	63	19	6	61	17	7	-
Thrombocytopenia	24	4	1	36	7	<1	<1
Hepatic							<1
ALT	68	8	2	72	10	1	
AST	67	6	2	78	12	5	
Alkaline Phosphatase	55	7	2	77	16	4	
Bilirubin	13	2	<1	26	6	2	
Renal							<1
Proteinuria	45	<1	0	32	<1	0	
Hematuria	35	<1	0	23	0	0	
BUN	16	0	0	15	0	0	
Creatinine	8	<1	0	6	0	0	
Non-laboratory[e]							
Nausea and Vomiting	69	13	1	71	10	2	<1
Pain	48	9	<1	42	6	<1	<1
Fever	41	2	0	38	2	0	<1
Rash	30	<1	0	28	<1	0	<1
Dyspnea	23	3	<1	10	0	<1	<1
Constipation	23	1	<1	31	3	<1	0
Diarrhea	19	1	0	30	3	0	0
Hemorrhage	17	<1	<1	4	2	<1	<1
Infection	16	1	<1	10	2	<1	<1
Alopecia	15	<1	0	16	0	0	0
Stomatitis	11	<1	0	10	<1	0	<1
Somnolence	11	<1	<1	11	2	<1	<1
Paresthesias	10	<1	0	10	<1	0	0

Grade based on criteria from the World Health Organization (WHO)
[a]N = 699-974; all patients with laboratory or non-laboratory data
[b]N = 161-241; all pancreatic cancer patients with laboratory or non-laboratory data
[c]N = 979
[d]Regardless of causality
[e]Table includes non-laboratory data with incidence for all patients ≥10%. For approximately 60% of the patients, non-laboratory events were graded only if assessed to be possibly drug-related.

Table 5

Selected WHO-Graded Adverse Events from Comparative Trial of Gemzar and 5-FU in Pancreatic Cancer

WHO Grades (% incidence)

	Gemzar[a]			5-FU[b]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[c]						
Hematologic						
Anemia	65	7	3	45	0	0
Leukopenia	71	10	0	15	2	0
Neutropenia	62	19	7	18	2	3
Thrombocytopenia	47	10	0	15	2	0
Hepatic						
ALT	72	8	2	38	0	0
AST	72	10	2	52	2	0
Alkaline Phosphatase	71	16	0	64	10	3
Bilirubin	16	2	2	25	6	3
Renal						
Proteinuria	10	0	0	2	0	0
Hematuria	13	0	0	0	0	0
BUN	8	0	0	10	0	0
Creatinine	2	0	0	0	0	0
Non-laboratory[d]						
Nausea and Vomiting	64	10	3	58	5	0
Pain	10	2	0	7	0	0
Fever	30	0	0	16	0	0
Rash	24	0	0	13	0	0
Dyspnea	6	0	0	3	0	0
Constipation	10	3	0	11	2	0
Diarrhea	24	2	0	31	5	0
Hemorrhage	0	0	0	2	0	0
Infection	8	0	0	3	2	0
Alopecia	18	0	0	16	0	0
Stomatitis	14	0	0	15	0	0
Somnolence	5	2	0	7	2	0
Paresthesias	2	0	0	2	0	0

Grade based on criteria from the World Health Organization (WHO)
[a]N = 58-63; all Gemzar patients with laboratory or non-laboratory data
[b]N = 61-63; all 5-FU patients with laboratory or non-laboratory data.
[c]Regardless of causality
[d]Non-laboratory events were graded only if assessed to be possibly drug-related.

Combination Use in Non-Small Cell Lung Cancer: In the Gemzar plus cisplatin vs. cisplatin study, dose adjustments occurred with 35% of Gemzar injections and 17% of cisplatin injections on the combination arm, versus 6% on the cisplatin only arm. Dose adjustments were required in greater than 90% of patients on the combination, versus 16% on cisplatin. Study discontinuations for possibly drug-related adverse events occurred in 15% of patients on the combination arm and 8% of patients on the cisplatin arm. In the Gemzar plus cisplatin vs. etoposide plus cisplatin study, dose adjustments occurred with 20% of Gemzar injections and 16% of cisplatin injections in the

Gemzar plus cisplatin arm compared with 20% of etoposide injections and 15% of cisplatin injections in the etoposide plus cisplatin arm. In patients who completed more than one cycle, dose adjustments were reported in 81% of the Gemzar plus cisplatin patients, compared with 68% on the etoposide plus cisplatin arm. Study discontinuations for possibly drug-related adverse events occurred in 14% of patients on the gemcitabine plus cisplatin arm and in 8% of patients on the etoposide plus cisplatin arm. The incidence of myelosuppression was increased in frequency with Gemzar plus cisplatin treatment (~90%) compared to that with the Gemzar monotherapy (~60%). With combination therapy Gemzar dosage adjustments for hematologic toxicity were required more often while cisplatin dose adjustments were less frequently required.

Table 6 presents the safety data from the Gemzar plus cisplatin vs. cisplatin study in non-small cell lung cancer. The NCI Common Toxicity Criteria (CTC) were used. The two-drug combination was more myelosuppressive with four (1.5%) possibly treatment-related deaths, including three resulting from myelosuppression with infection and one case of renal failure associated with pancytopenia and infection. No deaths due to treatment were reported on the cisplatin arm. Nine cases of febrile neutropenia were reported on the combination therapy arm compared to two on the cisplatin arm. More patients required RBC and platelet transfusions on the Gemzar plus cisplatin arm.

Myelosuppression occurred more frequently on the combination arm, and in four possibly treatment-related deaths myelosuppression was observed. Sepsis was reported in 4% of patients on the Gemzar plus cisplatin arm compared to 1% on the cisplatin arm. Platelet transfusions were required in 21% of patients on the combination arm and <1% of patients on the cisplatin arm. Hemorrhagic events occurred in 14% of patients on the combination arm and 4% on the cisplatin arm. However, severe hemorrhagic events were rare. Red blood cell transfusions were required in 39% of the patients on the Gemzar plus cisplatin arm, versus 13% on the cisplatin arm. The data suggest cumulative anemia with continued Gemzar plus cisplatin use.

Nausea and vomiting despite the use of antiemetics occurred slightly more often with Gemzar plus cisplatin therapy (78%) than with cisplatin alone (71%). In studies with single-agent Gemzar, a lower incidence of nausea and vomiting (58%-69%) was reported. Renal function abnormalities, hypomagnesemia, neuromotor, neurocortical, and neurocerebellar toxicity occurred more often with Gemzar plus cisplatin than with cisplatin monotherapy. Neurohearing toxicity was similar on both arms.

Cardiac dysrrhythmias of grade 3 or greater were reported in seven (3%) patients treated with Gemzar plus cisplatin compared to one (<1%) grade 3 dysrrhythmia reported with cisplatin therapy. Hypomagnesemia and hypokalemia were associated with one grade 4 arrhythmia on the Gemzar plus cisplatin combination arm.

Table 7 presents data from the randomized study of Gemzar plus cisplatin versus etoposide plus cisplatin in 135 patients with NSCLC for the same WHO-graded adverse events as those in Table 5. One death (1.5%) was reported on the Gemzar plus cisplatin arm due to febrile neutropenia associated with renal failure which was possibly treatment-related. No deaths related to treatment occurred on the etoposide plus cisplatin arm. The overall incidence of grade 4 neutropenia on the Gemzar plus cisplatin arm was less than on the etoposide plus cisplatin arm (28% vs. 56%). Grade 3 anemia and grade 3/4 thrombocytopenia were more common on the Gemzar plus cisplatin arm. Grade 3/4 nausea and vomiting were also more common on the Gemzar plus cisplatin arm. On the Gemzar plus cisplatin arm, 7% of participants were hospitalized due to febrile neutropenia compared to 12% on the etoposide plus cisplatin arm. More than twice as many patients had dose reductions or omissions of a scheduled dose of Gemzar as compared to etoposide, which may explain the differences in the incidence of neutropenia and febrile neutropenia between treatment

arms. Flu syndrome was reported by 3 % of patients on the Gemzar plus cisplatin arm with none reported on the comparator arm. Eight patients (12%) on the Gemzar plus cisplatin arm reported edema compared to one patient (2%) on the etoposide plus cisplatin arm.

Table 6
Selected CTC-Graded Adverse Events from Comparative Trial of Gemzar plus Cisplatin versus Single-Agent Cisplatin in NSCLC
CTC Grades (% incidence)

	Gemzar plus Cisplatin[a]			Cisplatin[b]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[c]						
Hematologic						
Anemia	89	22	3	67	6	1
Leukopenia	82	35	11	25	2	1
Neutropenia	79	22	35	20	3	1
Thrombocytopenia	85	25	25	13	3	1
Lymphocytes	75	25	18	51	12	5
Hepatic						
Transaminase	22	2	1	10	1	0
Alkaline Phosphatase	19	1	0	13	0	0
Renal						
Proteinuria	23	0	0	18	0	0
Hematuria	15	0	0	13	0	0
Creatinine	38	4	<1	31	2	<1
Other Laboratory						
Hyperglycemia	30	4	0	23	3	0
Hypomagnesemia	30	4	3	17	2	0
Hypocalcemia	18	2	0	7	0	<1
Non-laboratory[d]						
Hosp. For ADRs	48			30		
Sepsis	4			1		
RBC Transfusions	39			13		
Platelet Transfusions	21			<1		
Nausea	93	25	2	87	20	<1
Vomiting	78	11	12	71	10	9
Alopecia	53	1	0	33	0	0
Neuro Motor	35	12	0	15	3	0
Constipation	28	3	0	21	0	0
Neuro Hearing	25	6	0	21	6	0
Diarrhea	24	2	2	13	0	0
Neuro Sensory	23	1	0	18	1	0
Infection	18	3	2	12	1	0
Fever	16	0	0	5	0	0
Neuro Cortical	16	3	1	9	1	0
Neuro Mood	16	1	0	10	1	0
Local	15	0	0	6	0	0
Neuro Headache	14	0	0	7	0	0
Stomatitis	14	1	0	5	0	0
Hemorrhage	14	1	0	4	0	0
Dyspnea	12	4	3	11	3	2
Hypotension	12	1	0	7	1	0
Rash	11	0	0	3	0	0

Grade based on Common Toxicity Criteria (CTC). Table includes data for adverse events with incidence ≥10% in either arm.

[a]N = 217-253; all Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin at 100 mg/m^2 on Day 1 every 28 days.

[b]N =213-248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m^2 on Day 1 every 28 days.

[c]Regardless of causality

[d]Non-laboratory events were graded only if assessed to be possibly drug-related

Table 7

Selected WHO-Graded Adverse Events from Comparative Trial of Gemzar plus Cisplatin versus Etoposide plus Cisplatin in NSCLC

WHO Grades (% incidence)

	Gemzar plus Cisplatin[a]			Etoposide plus Cisplatin[b]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[c]						
Hematologic						
Anemia	88	22	0	77	13	2
Leukopenia	86	26	3	87	36	7
Neutropenia	88	36	28	87	20	56
Thrombocytopenia	81	39	16	45	8	5
Hepatic						
ALT	6	0	0	12	0	0
AST	3	0	0	11	0	0
Alkaline Phosphatase	16	0	0	11	0	0
Bilirubin	0	0	0	0	0	0
Renal						
Proteinuria	12	0	0	5	0	0
Hematuria	22	0	0	10	0	0
BUN	6	0	0	4	0	0
Creatinine	2	0	0	2	0	0
Non-laboratory[d,e]						
Sepsis	2			2		
RBC Transfusions	29			21		
Platelet Transfusions	3			8		
Nausea and Vomiting	96	35	4	86	19	7
Fever	6	0	0	3	0	0
Rash	10	0	0	3	0	0
Dyspnea	1	0	1	3	0	0
Constipation	17	0	0	15	0	0
Diarrhea	14	1	1	13	0	2
Hemorrhage	9	0	3	3	0	3
Infection	28	3	1	21	8	0
Alopecia	77	13	0	92	51	0
Stomatitis	20	4	0	18	2	0
Somnolence	3	0	0	3	2	0
Paresthesias	38	0	0	16	2	0

Grade based on criteria from the World Health Organization (WHO)

[a]N = 67-69; all Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1250 mg/m^2 on Days 1 and 8 and cisplatin at 100 mg/m^2 on Day 1 every 21 days.

[b]N = 57-63; all cisplatin plus etoposide patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m^2 on Day 1 and I.V. etoposide at 100 mg/m^2 on Days 1, 2, and 3 every 21 days.

[c]Regardless of causality

[d]Non-laboratory events were graded only if assessed to be possibly drug-related.

[e]Pain data were not collected

OVERDOSAGE

There is no known antidote for overdoses of Gemzar. Myelosuppression, paresthesias and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m^2 was administered by I.V. infusion over 30 minutes every 2 weeks to several patients in a Phase 1

study. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

DOSAGE AND ADMINISTRATION

Gemzar is for intravenous use only.

Adults

***Single-Agent Use**:*

Pancreatic Cancer—Gemzar should be administered by intravenous infusion at a dose of 1000 mg/m2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.

Dose Modifications—Dosage adjustment is based upon the degree of hematologic toxicity experienced by the patient (*see* Warnings). Clearance in women and the elderly is reduced and women were somewhat less able to progress to subsequent cycles (*see* Human Pharmacokinetics and Precautions).

Patients receiving Gemzar should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 8.

Table 8
Dosage Reduction Guidelines

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
≥1,000	and	≥100,000	100
500-999	or	50,000-99,000	75
<500	or	<50,000	Hold

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemzar should be administered with caution in patients with evidence of significant renal or hepatic impairment.

Patients treated with Gemzar who complete an entire cycle of therapy may have the dose for subsequent cycles increased by 25%, provided that the absolute granulocyte count (AGC) and platelet nadirs exceed 1500 x 10^6/L and 100,000 x 10^6/L, respectively, and if non-hematologic toxicity has not been greater than WHO grade 1. If patients tolerate the subsequent course of Gemzar at the increased dose, the dose for the next cycle can be further increased by 20%, provided again that the AGC and platelet nadirs exceed 1500 x 10^6/L and 100,000 x 10^6/L, respectively, and that non-hematologic toxicity has not been greater than WHO grade 1.

***Combination Use*:**

Non-Small Cell Lung Cancer—Two schedules have been investigated and the optimum schedule has not been determined (*see* Clinical Studies). With the 4-week schedule, Gemzar should be administered intravenously at 1000 mg/m^2 over 30 minutes on days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m^2 on day 1 after the infusion of Gemzar. With the 3-week schedule, Gemzar should be administered intravenously at 1250 mg/m^2 over 30 minutes on days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100 mg/m^2 should be administered intravenously after the infusion of Gemzar on day 1. See prescribing information for cisplatin administration and hydration guidelines.

Dose Modifications—Dosage adjustments for hematologic toxicity may be required for Gemzar and for cisplatin. Gemzar dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving Gemzar should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 8. For cisplatin dosage adjustment, see manufacturer's prescribing information.

In general, for severe (grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with Gemzar plus cisplatin should be held or decreased by 50% depending on the judgment of the treating physician. During combination therapy with cisplatin, serum creatinine, serum potassium, serum calcium, and serum magnesium should be carefully monitored (grade 3/4 serum creatinine toxicity for Gemzar plus cisplatin was 5% versus 2% for cisplatin alone).

Gemzar may be administered on an outpatient basis.

Instructions for Use/Handling—The recommended diluent for reconstitution of Gemzar is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemzar upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200 mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1 g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200 mg vial or 1.3 mL for the 1 g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

Reconstituted Gemzar is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.

When prepared as directed, Gemzar solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F) [*See* USP]. Discard unused portion. Solutions of reconstituted Gemzar should not be refrigerated, as crystallization may occur.

The compatibility of Gemzar with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

Unopened vials of Gemzar are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) [*See* USP].

Caution should be exercised in handling and preparing Gemzar solutions. The use of gloves is recommended. If Gemzar solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water. Although acute dermal irritation has not been observed in animal studies, two of three rabbits exhibited drug-related systemic toxicities (death, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Vials:

200 mg white, lyophilized powder in a 10 mL size sterile single use vial (No. 7501)
NDC 0002-7501-01

1 g white, lyophilized powder in a 50 mL size sterile single use vial (No. 7502)
NDC 0002-7502-01

Store at controlled room temperature (20° to 25°C) (68° to 77°F). The USP has defined controlled room temperature as "A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses."

Rx only

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